Self-Reported Physician Diagnosed Asthma with COPD is Associated with Higher Mortality than Self-Reported Asthma or þÿ C O P D A l o n e A P r o s p e c t i v e 2 4 - Y e a r S t u d y i n t h of Helsinki, Finland

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Self-Reported Physician Diagnosed Asthma with COPD is Associated with Higher Mortality than Self-Reported Asthma or COPD Alone – A Prospective 24-Year Study in the Population of Helsinki, Finland

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Self-Reported Physician Diagnosed Asthma with COPD is Associated with Higher Mortality than Self-Reported Asthma or COPD Alone – A Prospective 24-Year Study in the Population of Helsinki, Finland

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ABSTRACT

Asthma and COPD are common chronic obstructive respiratory diseases. COPD is associated with increased mortality, but for asthma the results are varying. Their combination has been less investigated, and the results are contradictory. The aim of this prospective study was to observe the overall mortality in obstructive pulmonary diseases and how mortality was related to specific causes using postal questionnaire data. This study included data from 6,062 participants in the FinEsS Helsinki Study (1996) linked to mortality data during a 24-year follow-up. According to self-reported physician diagnosed asthma, COPD, or smoking status, the population was divided into five categories: combined asthma and COPD, COPD alone and asthma alone, ever-smokers without asthma or COPD and never-smokers without asthma or COPD (reference group). For the specific causes of death both the underlying and contributing causes of death were used. Participants with asthma and COPD had the highest hazard of mortality 2.4 (95% CI 1.7–3.5). Ever-smokers without asthma or COPD had a 9.5 (3.7–24.2) subhazard ratio (sHR) related to lower respiratory tract disease specific causes. For asthma, COPD and combined, the corresponding figures were 10.8 (3.4–34.1), 25.0 (8.1–77.4), and 56.1 (19.6–160), respectively. Ever-smokers without asthma or COPD sHR 1.7 (95% CI 1.3–2.5), and participants with combined asthma and COPD 3.5 (1.9–6.3) also featured mortality in association with coronary artery disease. Subjects with combined diseases had the highest hazard of overall mortality and combined diseases also showed the highest hazard of mortality associated with lower respiratory tract causes or coronary artery causes.

ABBREVIATIONS: Cig: Cigarette; COPD: Chronic obstructive pulmonary disease; CVD: Cardiovascular disease; FEV_1: Forced Expiratory Volume in one second; FVC: Forced Vital Capacity; FinEsS: Finland, Estonia, and Sweden study on chronic obstructive pulmonary diseases; HR: Hazard Ratio; sHR: Subhazard Ratio; ICD-10: International Statistical Classifications of Diseases and Related Health Problems (Version 10)

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Introduction

The combination of asthma and Chronic obstructive pulmonary disease (COPD) in the same patient has been described before, yet it remains poorly described, with conflicting opinions on whether it should be addressed as merely two coexisting diagnoses [1] or as a separate heterogenous group of conditions [2]. Various studies have adopted varying definitions for asthma and COPD diagnoses, ranging from self-reported to spirometry confirmed diagnoses, differences in bronchodilator response test or inflammation criteria [3,4]. Lack of a clear definition has led also to different estimations on the prevalence of combined asthma and COPD in general populations. While the definition of the combined asthma and COPD may vary between studies, applying such concepts as ACO or ACOS, deteriorated quality of life and more exacerbations have

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been reported in this group compared to patients with only COPD or asthma [5–11].

Long-term prognosis for moderate to severe COPD is poor and highly dependent on smoking cessation [12,13]. In contrast, the prognosis of asthma in Finland has improved in the last decade, partly due to a national asthma program and increased treatment with inhaled corticosteroids [14]. However, individuals with combined diagnoses have a poorer outcome in those with late onset asthma [15].

Contradictory findings on the mortality of combined asthma and COPD have been reported in the literature. Some hospital-based studies [16–20] have indicated lower mortality compared to COPD alone, even if they had more exacerbations. On the other hand, a large population-based study from Denmark [15] reported higher overall mortality in combined asthma and COPD (3–4-fold) than in COPD alone (3-fold) when compared to healthy never-smokers. Another large registry study from Denmark [21] also reported high mortality ratios with patients who had both asthma and COPD diagnosis. Most of these studies have only addressed all-cause mortality, while one study [15] also reported specific respiratory disease mortality. Although COPD is recognized as a risk for cardiovascular disease (CVD) [22], no studies have analyzed CVD mortality in the combination of asthma and COPD.

A recent study suggested an increased risk for a new CVD in individuals with asthma alone or COPD alone, and the highest risk in those with combined disease [23,24]. Inflammatory pathways have been suggested as a possible mechanism explaining association between myocardial infarction and asthma [25]. Similar mechanisms could be involved in an association between combined asthma and COPD and ischemic heart disease [24], although both are associated with smoking.

Primarily we aimed to look at the differences in overall mortality between self-reported physician diagnosed asthma, COPD, and their combination in this 24-year follow-up study. Secondarily, we aimed to explore the disease-specific cause of death in self-reported physician diagnosed asthma, COPD and combined asthma and COPD.

Methods

This study includes the Finnish data from the FinEsS-Helsinki questionnaire study from 1996 out of which we chose questions to describe the participants at the baseline. These questions are shown in Table 1.

Subjects

The first phase of the study was performed between 1995 and 1997 with a population that was randomly selected by Statistics Finland, aged 20–69 years, in the city of Helsinki [26,27]. 8,000 postal questionnaires were sent in spring 1996 with 6,062 responders, 76% of those invited.

Further details on the background of the questionnaire used can be found in the supplementary part of the article.

Measurements and definitions of outcomes

Using the definitions shown in Table 2, the responders were divided into five groups: self-reported physician-diagnosed COPD or asthma or both (Combined), and participants without asthma or COPD were categorized by tobacco smoking status.

From the mortality data we acquired the deaths related to disease-specific causes as can also be seen in Table 2.

All assessments of death in Finland are sent to Statistics Finland where they are also verified by a forensic medicine expert. Statistics Finland also produces guidelines for physicians in the devising of death certificates and assessing causes of death.

More details on the mortality data and the definitions for causes of death can be found in the supplementary section (Table S1, supplementary material).

The study was approved by the ethics committee of the Department of Medicine, Helsinki University Central Hospital. The subjects filled in a written informed consent form.

Statistical analysis

We compared the demographic and symptom data at the baseline by using Fisher's exact and asymptotic Chi-square tests. For the age distributions tests, we applied Man-Whitney U test and Kruskal-Wallis test. Statistical significance for all the comparisons was set to 0.05.

Our primary mortality model was Cox proportional hazard model. A Cox model is a well-known statistical technique for examining the relationship between the survival time of a participant and explanatory variables (predictors and confounders). The outcome measures of these models are hazard ratios (HR) and their 95% confidence intervals. A HR is a ratio of two hazard rates. (For instance, a hazard rate for current smokers divided by a hazard rate for never smokers.) A hazard rate is a probability that a person at a time period t will die at that time period (by assuming he is alive before the time period t).

With this regression model we were able to adjust the survival model for several covariant variables and compare the hazards between the diagnostic groups. The follow-up study time was used as the basis of the time variable of the model. For the model, participants without asthma or COPD were split in two separate groups: ever-smokers and never-smokers. The latter (never-smokers without asthma or COPD) was chosen as the reference group for the analysis. The model was adjusted for age and sex, and in the supplementary part also for smoking. Study time was defined as the time in days starting from 1 January 1996 until emigration, death, or end of observation at 31 December 2019. The proportional hazard assumptions were fulfilled in the overall mortality model.

A secondary model was done with Fine-Gray regression analysis for the disease specific mortalities to compute subhazard ratios, the choice to use this analysis was made based on the consideration of competing events as well as we also used contributing factors as an end-event. These were

Table 1. FinEsS-questionnaire questions in English.

Smoking habit	Current smoker	Do you smoke currently? (answer yes even if you have quit in the past 12 months)	Yes/No
	Cigars per day	How many cigars, cigarettes or pipefuls have you smoked on average per day? (answer only if you answered Yes to do you smoke currently)	Less than 5 5–14 15 or more
	Ex-smoker	Have you been a smoker before, but quit smoking over 12 months ago? (answer only if you answered No to the question of currently smoking)	Yes/No
Questions related to asthma:	Asthma diagnosis by a physician	Have you been diagnosed as having asthma by a physician	Yes/No
	Asthma medicine use	Do you use any asthma medicine? (Medicine used was not defined)	Yes/No
	Asthma symptoms	Have you, during the last 12 months, had intermittent attacks or periodic breathlessness, with or without cough or wheezing/whistling in your chest?	Yes/No
	Allergic rhinitis	Have you ever had allergic rhinitis (e.g. hay fever) or allergic eye condition?	Yes/No
Questions related to COPD:	COPD diagnosis by a physician	Have you been diagnosed as having chronic bronchitis or emphysema by a physician?	Yes/No
	Chronic cough	Have you had longstanding cough during the last year?	Yes/No
	Sputum production	Do you usually have phlegm when coughing or do you have phlegm in your chest, which is difficult to bring up?	Yes/No
Question related to physical status:	Shortness of breath (SOB)	Do you have shortness of breath or do you have to walk slower due to shortness of breath when you are walking on even ground with your age group at a normal pace	Yes/No

The original questionnaire had all the questions in both Finnish and Swedish and are translated here to English.
COPD: Chronic obstructive pulmonary disease.

Table 2. Definitions of diagnosis, smoking and mortality.

Diagnosis definitions	Asthma	Answered yes to asthma diagnosed by a physician and no to COPD diagnosed by physician.
	COPD	Answered yes to COPD diagnosed by a physician and no to asthma diagnosed by a physician and was an ever-smoker.
	Combined	Answered yes to both; asthma diagnosed by a physician; COPD diagnosed by a physician.
	Without asthma or COPD	Answered no to both asthma and COPD diagnosed by a physician.
Smoking definitions:	Never-smoker	Answered no to both *Current smoker* and *Ex-smoker* questions.
	Ever-smoker	Answered yes to either *Current smoker* or *Ex-smoker* question.
Mortality definitions:	Chronic lower respiratory tract disease specific, (J40-J47)	Has either the underlying cause of death or any contributing cause of death marked in the registry with ICD-10: J40-J47.
	Coronary artery disease specific mortality, (I20-I25)	Has either the underlying cause of death or any contributing cause of death marked in the registry with ICD-10: I20-I25.

COPD: Chronic obstructive pulmonary disease; ICD-10: International Statistical Classifications of Diseases and Related Health Problems.

adjusted for age and sex, and in the supplementary part also for smoking. The reference group was the never-smokers without asthma or COPD.

We had to use restricted mean survival time in Kaplan-Meier estimates as no diagnosis category reached the 50% survival probability and only combined asthma and COPD and COPD alone reached the 75% survival probability. For the Kaplan-Meier estimates, we stratified the data to 5 age groups: 20–29-, 30–39-, 40–49-, 50–59-, 60–69-year-old at baseline. This stratification allowed for the comparison of the mean survival time as the various diagnosis groups had similar median ages at the starting point of 1996. Pairwise comparison for Table 5 was computed with Logrank (Mantel-Cox) test.

All statistical analyses were carried out using IBM SPSS Statistics version 27 (IBM Corp, New York, NY, USA) and, for the Fine-Gray model, StataCorp. 2021. *Stata Statistical Software: Release 17*. College Station, TX: StataCorp LLC.

Results

Self-reported diagnoses

The study cohort was originally 6,062 participants, out of which 147 subjects were removed due to incomplete filling of the asthma and COPD questions in the postal questionnaire, leaving 5,915 participants in the analysis. The demographic as well as symptoms and smoking data between diagnosis groups are given in Table 3. The prevalence of self-reported symptoms varied substantially between the reported diagnoses.

The combined asthma and COPD group had the highest prevalence of symptoms and asthma medicine use as well as being the oldest group at baseline, they also had a higher prevalence of current smoking compared to the asthma group. COPD had the highest daily number of cigarettes smoked. Asthma was more common in women than men, while combined asthma and COPD was more common in men, while there was no difference by sex regarding COPD diagnosis.

Men were more likely to smoke than women, and had higher overall mortality, however women were more symptomatic with both asthma symptoms as well as symptoms associated with COPD.

During the median follow-up time of 24.0 years (range of 0.1–24.0 years), 970 deaths (16%) occurred among the participating cohort. The highest mortality during the follow-up was in the combined asthma and COPD group with 49% mortality out of which 44% were registered with specific Chronic lower respiratory tract disease (J40-J47)

Table 3. Demographic data, smoking habits, use of asthma medication and symptom prevalence in relation to diagnosis and sex.

	Female	Male	*p*	Never-smoker without asthma or COPD	Ever-smoker without asthma or COPD	Asthma	Combined asthma and COPD	COPD	*p*
n (5915) (100 %)	3,374(57)	2,541(43)		2,678 (46.0)	2,741 (46.0)	314 (5.3)	69 (1.2)	113 (1.9)	
Age Median at 96 (y) (IQR)	41 (22)	42 (21)	**0.033**	40 (22)	42 (19)	41(23)	59(18)	48(21)	**<0.001**
Sex (f/m)	3,374/0	0/2,541		1,717/961	1,350/1,391	215/99	30/39	62/51	**<0.001***
Current smoking status 1996			**<0.001**						**<0.001***
Never-smoker (%)	1,841 (55)	1,001 (40)		2,700 (100)	0 (0)	157 (50)	22 (32)	0 (0)	
Ex-smoker (%)	468 (14)	508 (20)		0 (0)	876 (32)	57 (18)	19 (28)	24 (21)	
Current smoker (%)	1,056 (31)	1,024 (40)		0 (0)	1,865 (68)	99 (32)	27 (40)	89 (79)	
Current daily smoking			**<0.001**						**<0.001***
5 cig. per day (%)	262 (25)	199 (19)		0 (0)	425 (23)	23 (23)	0 (0)	13 (15)	
5–14 cig. per day (%)	459 (44)	347 (34)		0 (0)	720 (39)	51 (52)	12 (44)	23 (26)	
>14 cig. per day (%)	335 (32)	476 (47)		0 (0)	720 (39)	25 (25)	15 (56)	53 (60)	
Asthma medicine use (%)	222 (7)	112 (4)	**<0.001**	26 (1)	27 (1)	214 (70)	56 (82)	11 (10)	**<0.001***
Asthma symptoms (%)	497 (15)	287 (11)	**<0.001**	159 (6)	248 (9)	226 (73)	62 (90)	50 (46)	**<0.001***
Allergic rhinitis (%)	1,336 (40)	834 (33)	**<0.001**	952 (36)	880 (32)	229 (74)	47 (71)	62 (55)	**<0.001***
Chronic cough (%)	696 (21)	451 (18)	**0.005**	382 (15)	529 (20)	118 (38)	49 (72)	69 (62)	**<0.001***
Productive cough (%)	903 (28)	642 (26)	0.158	459 (18)	791 (30)	149 (49)	56 (85)	90 (80)	**<0.001***
Shortness of breath (%)	527 (16)	261 (10)	**<0.001**	211 (8)	354 (13)	116 (37)	50 (75)	57 (51)	**<0.001***
All mortalities in follow-up (%)	444 (13)	526 (21)	**<0.001**	314 (12)	534 (20)	51 (16)	34 (49)	37 (33)	**<0.001***
Chronic lower respiratory tract disease specific (%)	36/444 (8)	45/526 (9)	0.817	5/323 (2)	46/534 (9)	7/51 (14)	15/34 (44)	8/37 (22)	**<0.001***
Coronary artery specific contribution (%)	88/444 (20)	157/526 (30)	**<0.001**	67/323 (21)	129/534 (24)	15/51 (29)	16/34 (47)	9/37 (24)	**0.019***

Missing 147 (2.4%) cases with either no answer or only a partial answer to physician diagnosed asthma or physician diagnosed COPD or had COPD without smoking.

*Asymptotic Chi-Square *p*-value only.

Combined asthma and COPD Self-reported physician diagnosed asthma and COPD from 1996; *Shortness of breath* defined as having shortness of breath when walking on a flat ground with own age group; IQR: Inter-quartile range; Cig.: Cigarette; Std: Standard deviation.

Significant *p*-values are bolded.

either as a contributing factor or an underlying cause of death. Some 47% of combined asthma and COPD participants were registered with coronary artery disease as cause of death (I20-I25). COPD alone had the second highest overall mortality at 33%.

Adjusted cox regression analysis of deaths over study time with smoking stratification and pairwise comparisons

Table 4 shows the results of the cox regression analysis of overall, chronic lower respiratory tract disease and coronary artery mortality over the whole study time of 24.0 years.

In analysis of all-cause mortality, those with combined asthma and COPD had a 2.4-fold hazard, those with COPD alone a 2.1-fold and compared to never-smokers without asthma or COPD. In chronic lower respiratory tract disease specific model, all the diagnostic groups showed increased subhazard ratios for mortality related to J40-J47 causes, with combined asthma and COPD carrying 56-fold, COPD 25-fold and Asthma 11-fold subhazard compared to never-smokers without diagnosis. Ever-smokers without asthma or COPD had a 1.8-fold subhazard for mortality related to coronary artery disease while combined group had a 3.5-fold subhazard.

Survival plots for can be seen in Figure 1(a,b). These plots represent the age and sex adjusted regression models.

Mean survival time

The mean survival time for overall mortality has been estimated as restricted mean survival time with the Kaplan-Meier estimator (Table 5 and Figure 2). The results have been stratified for 10-year age groups as the different diagnosis groups had differing median ages.

Within all three oldest age groups combined asthma and COPD had the lowest mean survival time although for the 40–49 age group the results were inconclusive due to small number of deaths. COPD group had the second lowest estimate for all other age groups except 60–69-year-olds wherever-smokers without asthma or COPD had the second lowest survival time. In all age groups ever-smokers without asthma or COPD had lower mean survival time than never-smokers without asthma or COPD.

The different classes of mortality in two oldest age groups stratified by ever smoking as well as according to sex are presented in Tables S2 and S3, supplementary material showing that among ever-smokers combined asthma and COPD had the lowest survival time as well as showing that this pertains in both sexes with men also showing lower mean survival estimates.

Table 4. Adjusted regression analyses for overall and mortality related to disease specific causes.

		Overall mortality			
Hazard ratio (HR)*	*n*	*n* events (%)	HR	95%	CI
Never-smoker without asthma or COPD	2,678	314 (12)	1	Reference	
Ever-smoker without asthma or COPD	2,741	534 (19)	**1.80**	**1.56**	**2.08**
Asthma	314	51 (16)	1.31	0.98	1.77
COPD	113	37 (33)	**2.09**	**1.48**	**2.94**
Combined asthma and COPD	69	34 (49)	**2.44**	**1.70**	**3.48**
Subhazard ratios**		Chronic lower respiratory tract disease specific (J40-J47)			
Never-smoker without asthma or COPD	2,678	5 (2)	1	Reference	
Ever-smoker without asthma or COPD	2,741	46 (9)	**9.46**	**3.69**	**24.2**
Asthma	314	7 (14)	**10.8**	**3.43**	**34.1**
COPD	113	8 (22)	**25.0**	**8.07**	**77.4**
Combined asthma and COPD	69	15 (44)	**56.1**	**19.6**	**160**
Subhazard ratios**		Coronary artery disease specific (I20-I25)			
Never-smoker without asthma or COPD	2,716	67 (21)	1	Reference	
Ever-smoker without asthma or COPD	2,741	129 (24)	**1.75**	**1.30**	**2.34**
Asthma	314	15 (29)	1.77	0.98	3.06
COPD	113	9 (24)	1.73	0.88	3.57
Combined asthma and COPD	69	16 (47)	**3.45**	**1.90**	**6.26**

Hazard ratios* were computed with the Cox regression model.
Subhazard ratios** were computed with Fine-Gray regression model.
Hazard of death during the study time is expressed as hazard ratio (HR) with 95% confidence intervals.
The regression models were adjusted for age and sex.
COPD: Chronic Obstructive Pulmonary Disease; Combined: self-reported physician diagnosed asthma and COPD; HR: Hazard Ratio.
The statistically significant Hazard ratios and their confidence interval values are bolded.

Discussion

We studied the differences of mortality between self-reported physician diagnosed asthma, COPD, and the combination of self-reported physician made diagnoses of asthma and COPD in a 24-year prospective study. Asthmatics and COPD patients, as well as ever-smokers without asthma or COPD, had an increased mortality related to chronic lower respiratory tract disease compared to never smokers without asthma or COPD (Table 4). We also found that combined asthma and COPD diagnoses had the highest hazard for overall mortality and mortality related chronic lower respiratory tract disease as well as the highest mortality related to coronary artery disease. To our knowledge, this is the first study to report coronary artery disease contribution to death in combined COPD and asthma.

Chronic obstructive pulmonary disease (COPD) is characterized by chronic airway inflammation and irreversible airflow limitation with emphysematous alveolar wall destruction in part of those affected, and the disease usually is associated with tobacco smoking [1]. Combined asthma and COPD has features from both COPD and asthma represented with partial reversibility of obstruction, airway hyperreactivity, sputum eosinophilia, but the definitions are varying [2–4]. In the present study, even when the COPD group included only ever-smokers and the combined group also included never-smokers, the latter had worse prognosis. This might indicate that at least part of the increase of mortality in the combined diagnoses could be due to the cross-effect of smoking and a progressed inflammation of bronchial mucosa in asthma, although the study did not include measurement of inflammatory markers.

Asthma is characterized by variable reversible obstructive airflow limitation and symptoms, while COPD is more often associated with irreversible progressive airflow limitation. The dual diagnosis of asthma and COPD has both a reversible and an irreversible component. There exist variations on the causes of asthma, its progression, triggering factors and reversibility. Chronic obstruction has been observed in some asthma patients who are resistant to asthma medication. The explanation for this has been thought to be in the airway remodeling due to chronic inflammation [28–30]. The remodeling can lead to a progressive obstructive disease, causing permanent lowering of lung function [31,32] as seen in chronic obstructive bronchitis and emphysema.

Asthma alone does not seem to have a significant effect on mortality in the adjusted model, however, combined with COPD it does have. The cause of this could be due to differences in the character and location of the inflammation (airway inflammation in asthma and systemic inflammation in COPD) [1]. In addition, lung function could be more preserved in asthma than in COPD. The patients with asthma probably smoked less and have been in a better follow-up and treatment than those with COPD partly based on the drug compensation practices in Finland as discussed later.

Cumulative tobacco smoking and increased age are important risk factors for COPD, as the nonreversible airway obstruction with inflammation takes time to develop and progress. This can also be seen in earlier study, where those with combined asthma and COPD have been reported to be older than those with asthma or COPD alone [15]. In our study, the median age of COPD and combined groups were 10 and 20 years older than the other groups. To accommodate this, the Cox regression model was adjusted for age, however, in the Kaplan-Meier estimator age cannot be adjusted similarly. To overcome this, we stratified the ages of the whole group into 10-year age groups (Table 5, Figure 2, and Tables S2 and S3, supplementary material). Within this stratification we could compare the mean survival time

Table 5. Mean survival time stratified by age groups.

	Overall mortality						
	n cases	*n* deaths	Mean survival time (Years)	Standard deviation	95%	CI	Pairwise comparisons
Age at 1996 (years)							*p*
40–49	1,345	171					
Never-smoker without asthma or COPD	551	51	23.0	0.2	22.7	23.3	ref
Ever-smoker without asthma or COPD	681	102	**22.7**	0.2	22.4	23.0	**0.003**
Asthma	70	8	22.9	0.5	22.0	23.8	0.569
COPD	33	8	**22.0**	0.8	20.4	23.7	**0.005**
Combined asthma and COPD	10	2	20.4	2.3	15.9	25.0	0.198
50-59	1,098	285					
Never-smoker without asthma or COPD	449	70	22.6	0.2	22.3	23.0	ref
Ever-smoker without asthma or COPD	564	186	**21.0**	0.2	20.5	21.5	**<0.001**
Asthma	47	12	21.7	0.7	20.4	23.0	0.066
COPD	23	11	**19.0**	1.3	16.4	21.5	**<0.001**
Combined asthma and COPD	15	6	**17.9**	2.2	13.6	20.4	**0.002**
60-69	745	428					
Never-smoker without asthma or COPD	350	168	20.1	0.3	19.4	20.6	ref
Ever-smoker without asthma or COPD	286	192	**16.8**	0.4	15.9	17.7	**<0.001**
Asthma	52	26	19.4	0.9	17.7	21.1	0.627
COPD	25	16	17.4	1.4	14.7	20.0	**0.041**
Combined asthma and COPD	33	26	**15.4**	1.2	13.1	17.8	**<0.001**

p-values are computed as factor level pairwise comparisons with Mantel-Cox.
COPD: chronic obstructive pulmonary disease; Combined: self-reported physician diagnosed asthma and COPD; ref: reference group for pairwise comparisons. The values that were statistically significant in the pairwise comparison are bolded.

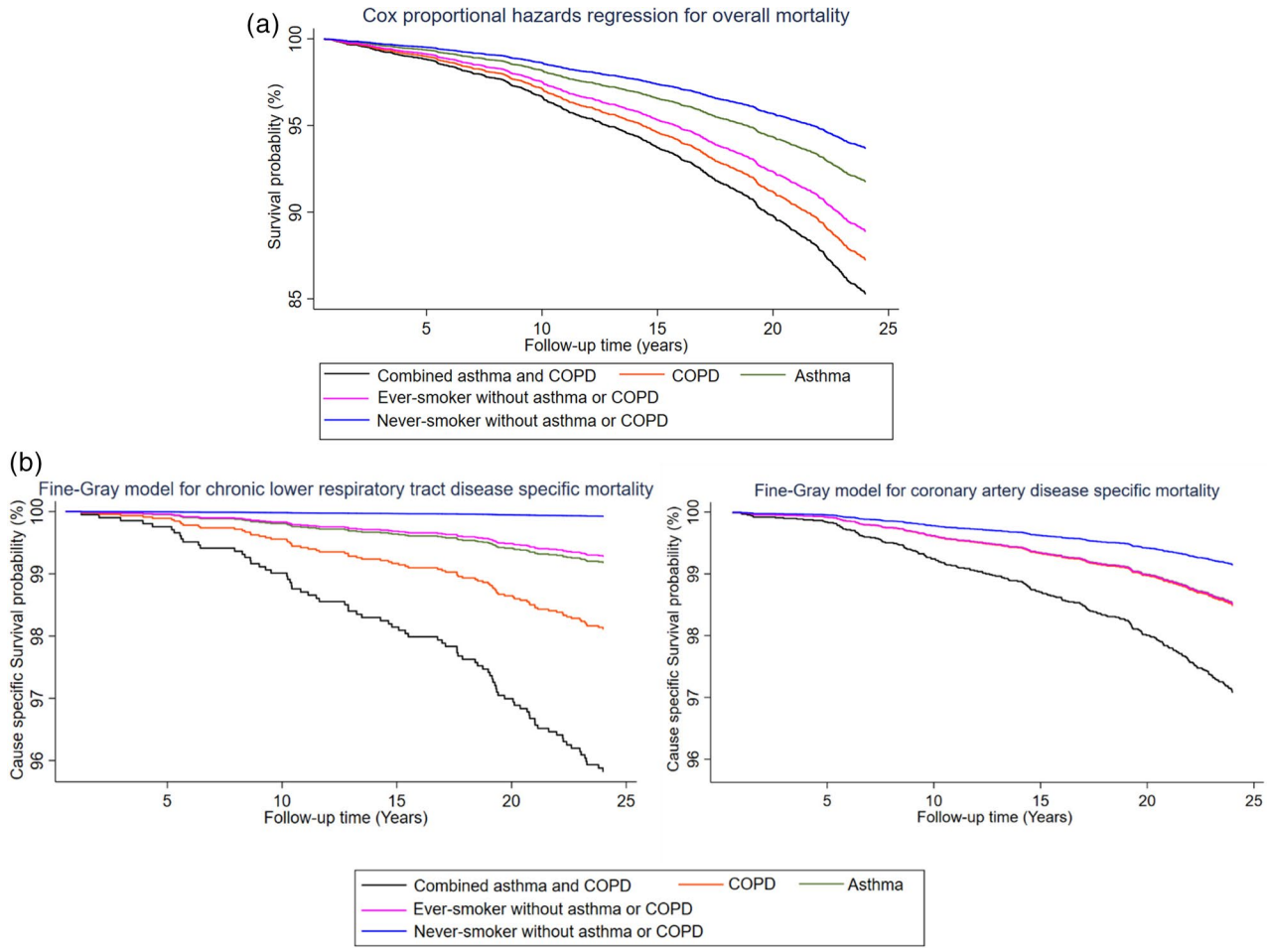

Figure 1. (a) Overall survival probability categorized by Diagnoses in 1996. (b) Disease specific survival probabilities categorized by Diagnoses in 1996.

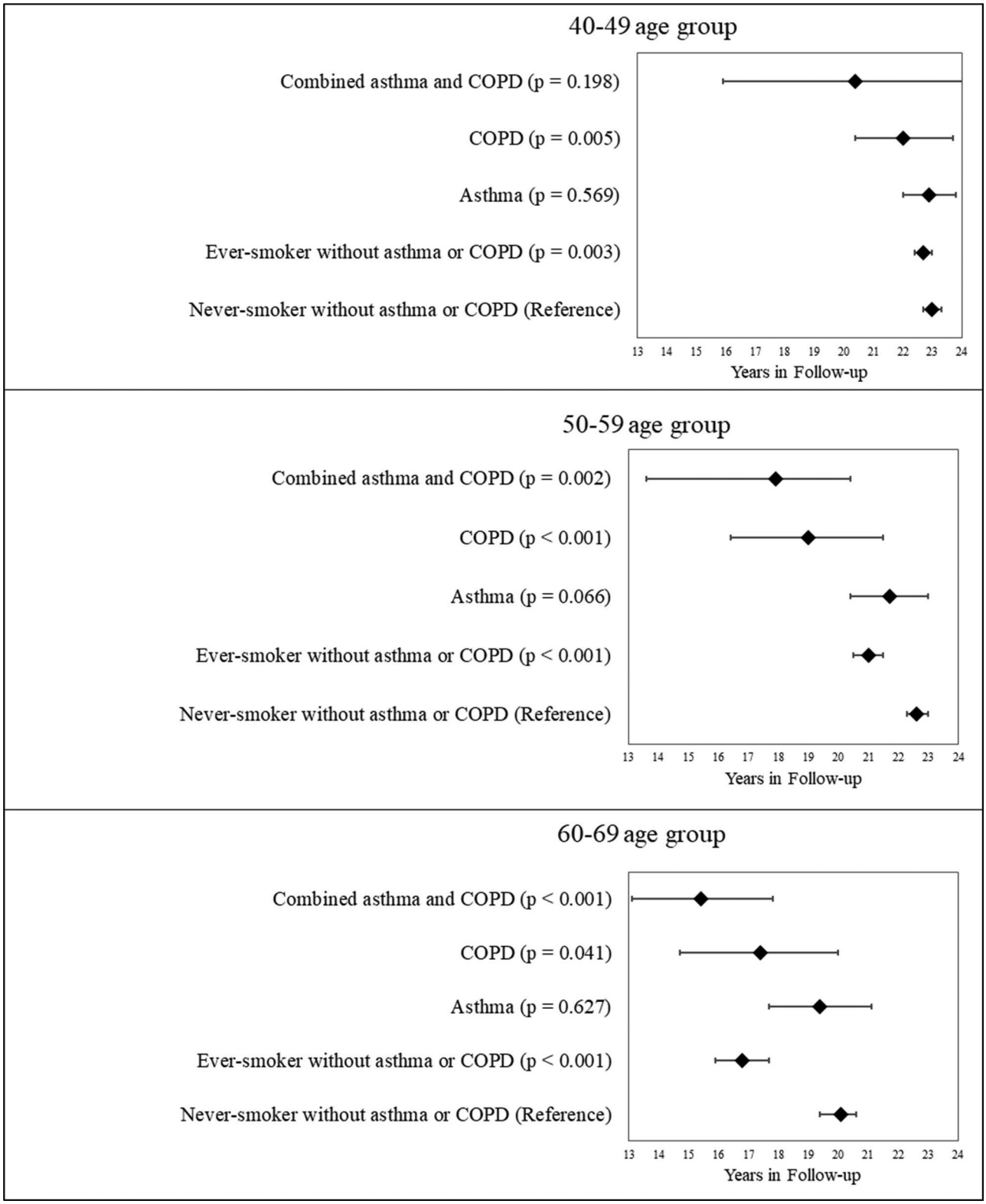

Figure 2. Mean survival times with 95% confidence intervals computed with the Kaplan-Meier estimator.

inside the different age groups. The stratified results show that COPD, combined asthma and COPD and ever-smokers without asthma or COPD had the lowest mean survival times, and that survival time was even lower when a further stratification was done with the never-smoker/ever-smoker variables. Compared to women, men were also more affected by these diseases as well as by smoking, suggesting a higher amount of pack years with male ever smokers.

Tobacco smoking is a known risk for coronary artery disease [33] and CVD mortality [34], and smoking cessation has been shown to reduce the risk of coronary artery disease mortality [35]. Combined asthma and COPD and COPD

alone have also been shown to have an increased hazard of coronary artery disease and heart failure, need for hospitalization due to coronary artery disease [24]. Underlying and contributing causes of death were analyzed for the subjects of the present study, and we found an increase in coronary artery disease specific mortality for combined asthma and COPD, and ever-smokers without diagnosis, the former having the highest hazard ratio.

The effect of smoking on mortality is the strongest in the chronic lower respiratory tract disease specific model, where all the diagnostic groups and the ever-smoker group had very high disease specific subhazard ratios. This result is similar to the previous study by Lange et al. [15] and furthermore shows that over 40% of deaths in the combined group are connected to chronic lower respiratory tract disease causes and is even higher than in the COPD group.

The present study suggests that combined asthma and COPD has the highest risks for overall, respiratory specific and coronary artery specific mortality among chronic obstructive pulmonary disease. The basis for this at least partly is related to smoking, although part of the patients with this combination were not known to be smokers. A probable basis of development of the combined disease is increased bronchial or bronchiolar inflammation associated with smoking or poor treatment response in asthma. The study also points to a systemic nature of the combined disease, being not only a pulmonary disease but also affecting the vasculature of the patient. The study also warrants further study on this combination disease, and efforts to prevent the development of this combination disease and the increased mortality associated with it.

Strengths and limitations

The main strength of our study was a large cohort of 6,062 persons contributing with data in a well responded postal questionnaire (76% response rate) and a long follow-up time.

The cause of death registry in Finland is gathered by Statistics Finland and all entries to it are verified by a forensic medicine expert increasing the validity of the registry data, as well as giving it a good coverage of all deaths in Finland. However, it is possible that a small number of deaths in cohort have gone unregistered due to the participant moving outside of Finland and the information of death not reaching the Finnish authorities. The guidelines for certificates of deaths have changed during the 24-year follow-up with increased information over filling the certificate of death given to the attending physicians. It is possible that these changes have influenced the disease specific mortality results with a relative increase in the number end-events in the last years of the follow-up.

The diagnosis of asthma in Finland is tied with the reimbursement of asthma medicine and as such has had a requirement of demonstration of reversible obstruction either with Peak Expiratory Flow-measurements (PEF) or spirometry or histamine or methacholine challenge test or exercise test. Furthermore, before the mid-90's most cases of asthma were diagnosed and treated by pulmonologists rather than general practitioners [36]. In previous research, most (90%) of the those who get reimbursed for asthma medication also reported a physician made asthma diagnosis [37]. With the strict functional diagnostic criteria for asthma, the diagnosis is reliable in Finland, however there may also be minor underdiagnosis of mild asthma due to these criteria in comparison to countries where the basis of asthma diagnosis has also been just the existence of symptoms.

In COPD, the basis of medical reimbursement has been FEV_1 < 40% of predicted, and the diagnosis of less severe COPD has been based on typical disease characteristics with a history of smoking and lack of significant variation of airflow limitation. Therefore, as the diagnostic practice in obstructive pulmonary diseases in Finland is stricter than in some other countries, also the self-reported physician made diagnoses are more reliable. However, this may also have caused subjects with COPD to receive medical treatment later, influencing on the prognosis of the disease.

As the study cohort is formed from old postal questionnaire answers, the question on COPD was based on an older definition of COPD which may have also included cases with chronic bronchitis not necessarily with obstruction. However, the question used corresponds to the diagnostic practices of the 1990s [38,39] and cannot be checked afterwards. This could, however, explain some lower-than-expected results in the COPD only group. To enhance the validity of the COPD diagnosis, the COPD only group was stratified to contain only the ever-smokers who answered yes to being diagnosed COPD by a physician. Though this removal limits the study of COPD alone participants only to smoking causes. On the other hand, it is possible that there could also be some over-diagnosis of COPD by the physicians, as documented associated with the application of the GOLD (FEV_1/FVC) cut off 0.7 criterion of COPD [40,41]. The diagnoses of asthma and COPD in Finland are diagnosed according to both symptoms and lung function tests results and thus major misdiagnoses of asthma with COPD are unlikely.

A response (selection) bias may also be present, as it is known that people of different sex and age may respond variedly to questionnaire studies, with younger men being likelier non-responders.

We could not adjust for Body Mass Index (BMI), as such measures were lacking for a large proportion of the participants. Thus, the results could be influenced by residual confounding by BMI as an earlier study has found increased respiratory mortality with increased BMI [42].

In the main model we made a choice not to use smoking as an adjusting variable which was in part done to be in-line with the previous study by Lange et al. [15]. This also enabled us to compare the groups for smoking status in a Kaplan-Meier estimator. This may have emphasized the results in those with asthma alone and combined asthma and COPD both of which also included smokers and nonsmokers. However, the results of the model adjusted for smoking can be found in supplementary tables (Table S4, supplementary material) and the estimates persisted in the combined group even when adjusted for smoking.

Conclusions

The combined diagnosis of asthma and COPD has a greater hazard for mortality and a lower mean survival time than either COPD or asthma diagnosis alone has, these results also pertained for the combined group when adjustment was made for smoking. We also found that combined asthma and COPD in the same person is associated with higher coronary artery mortality which is logical although not documented earlier.

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Declaration of interest

The authors declare that they have nothing to disclose.

Ethics approval

The study was approved by the ethics committee of the Department of Medicine, Helsinki University Central Hospital. The subjects filled in a written informed consent form.

Consent for publication

All participants of the study have signed an informed consent for research and publication.

Authors contribution

JJ has written the first version of the manuscript and performed the statistical analyses. JJ, PP, PK and RL have designed the present study. AS conceptualized and organized the original FinEsS-study in Finland in 1996. PP organized the mortality data collection from Statistics Finland. All participants have read, revised, and accepted the manuscript.

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